REMARKS

Entry of the foregoing amendments, reconsideration and re-examination of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in light of the remarks which follow, are respectfully requested.

By the present amendments, the non-elected claims have been cancelled to expedite prosecution. Claims 1, 24, 28, 41 and 45 are amended herein to overcome outstanding §112 rejections. Non-elected claims 3, 10-13, 15-23, 30-33, 38-40 and 42-44 are cancelled. Also, claims 37 and 49 are cancelled.

At the outset, prior to addressing the outstanding rejections, the Examiner is again respectfully thanked for the previous personal interview. During that interview the Examiner acknowledged that the then-cited prior art did not teach or suggest antibody dimers comprised of two different intact antibody molecules, each having retained and different antigen-binding properties. A preliminary amendment was filed based on this understanding. A rejection followed after that preliminary amendment which is addressed herein. It is believed that rejections were made because the Examiner believed that Applicants claims did not clearly define the claimed invention, in particular that the dimers produced by the subject method comprise two different intact antibodies. It is anticipated that this ambiguity is cured by the present amendments.

The objection to non-elected claims is noted. This objection is moot in view of the present amendment, canceling these claims.

The objection to the oath is again noted. A new oath will be provided shortly.

Claims 45 and 46 stand rejected for failing to specify that the location of the introduced cysteine residue does not adversely affect the ability of antibody to bind antigen after dimerization. This rejection is moot as claim 45 has been amended to contain this limitation. Withdrawal of the §112 first paragraph rejection of claims 45 and 46 is requested.

Claim 35 stands rejected as allegedly requiring the availability of deposited materials (hybridomas) that express specific antibodies. This rejection is respectfully traversed on the basis that the cited patents, incorporated by reference herein, i.e., U.S. Patent 5,830,698 and 6,011,138 provide the complete DNA and amino acid sequences for the C2B8 (Rituxan®) and p5I.8 antibodies. In fact the '138 patent was granted, and contained claims to this antibody,

antibodies based on the disclosed sequences in the cited patents absent undue experimentation.

Claims 37, 45 and 46 stand rejected under 35 U.S.C. §103 based on Caron et al., in view of Fanger et al. and Cumber et al., in view of Reff et al. The rejection is maintained because "[t]he rejected claims only require a dimeric antibody with two specificities or a heterodimeric antibody". This rejection must be vacated as claim 45 and 46 are amended herein to make absolutely clear that an IgG IgG dimeric antibody containing two intact IgG's is produced by the claimed methods. Also, claim 37 is cancelled. Thus this rejection should be moot.

Claims 1-2, 4-9, 14, 24-29, 34-37, 41 and 47-49 stand rejected under 35 U.S.C. §112 second paragraph as being indefinite. This rejection is respectfully traversed to the extent it may be applicable to the amended claims.

Claims 1-2, 4-9, 14, 24-29, 34-37, 41 and 47-49 are asserted to be unclear as to the intent of the reducing step. Applicants respectfully advise that the claims make clear that reduction is to "enhance the formation of antibody dimers". Thus, it would be abundantly clear to a skilled artisan that the introduced cysteine is reduced, is a residue that after reduction promotes dimerization. Indeed, it is unclear how one skilled in the art could possibly misconstrue the claims especially when the claims are read in light of the specification which goes into greater detail as to the incorporation of the cysteine residue in an antibody heavy chain in order to facilitate dimerization with another antibody. Applicants respectfully remind the Examiner that claims are not to be read in a vacuum, but instead construed based on the teachings of the specification as they would be by a skilled artisan.

The objection with respect to the failure to recite the presence of a thiol reactive group in clause (v) is moot based on the present amendment.

The objection to claim 28 and 41 is moot as these claims not depend on claim 45, an elected claim.

The objection to claims 1-2, 4-9, 14, 24-29, 34-37, 41, 47-49 based on the phrase "antibody molecule heavy chain that has binding specificity" is moot as the claims have been amended to clarify that this binding specificity is when the antibody is "paired with a corresponding antibody light chain" (having specificity to same antigen when paired

Claims 1-2, 4-9, 14, 24-29, 34-37, 41 and 47-49 stand rejected as being non-enabled because they are allegedly not limited to the conditions that result in antibody dimers as claimed. It is anticipated that this rejection should be moot as independent claims 1, 24 and 45 all make clear that a first intact antibody containing an introduced cysteine residue, in the heavy chain, is reduced, and contacted with a second antibody, containing a thiol reactive group, under conditions that result in an antibody dimer, containing two intact antibody molecules, each having different, retained antigen binding properties.

Based on Applicant's careful review and understanding of the §112 scope of enablement rejection it is believed that Applicants have amended their claims consistent with the Examiner's indication of what he acquiesces is, at least, enabled by the subject application. Withdrawal of the rejection is respectfully requested.

Claims 1-2, 4-9, 14, 24-29, 34-37, 41 and 47-49 stand rejected under 35 U.S.C. §103 based on Caron et al., in view of Fanger et al., Cumber et al., Reff et al., (U.S. Patent 6,011,138), Reff et al., (Blood (1994)) and the Pierce Catalog. This rejection is respectfully traversed.

Essentially applicants traverse the rejection on the basis that none of the prior art, by the Examiner's own admission teaches or suggests an antibody heterodimer as claimed. Rather, Caron et al., teaches a dimeric IgG that is monomeric, and wherein the dimerization method does not include the addition of thiol reactive group.

Fanger et al., is even more remote as it does not even deal with antibody dimers, rather it relates to bi-specific antibodies.

Likewise Cumber et al., pertains to bi-specific antibodies produced by use of chemical cross-linkers. The Pierce Catalog is cited based on its disclosure of various hetrobifunctional cross-linkers.

Finally, the Reff references are cited based on their disclosure of the specific anti-CD20 and anti-CD23 antibodies used to produced antibody dimers exemplified in this application.

Essentially, the Examiner suggests that the claims are rendered obvious over the prior art because of second statements made by Caron (relating to dimers), i.e., that "multimeric constructs of IgG may have advantages relative to those forms that are found naturally" and

This rejection is respectfully traversed on the basis that it is based on the improper "obvious to try" standard. Indeed, the prior art cited is not at all clear whether antibody dimeric can be produced that possess advantages properties, or that antibody multimers even possess enhanced effectiveness. Without this being clear, it is hardly understood how the preparation of antibody dimers as claimed would have been obvious.

Also, the rejection is traversed on the basis that it could not have been anticipated that antibody dimers could be obtained that bind two different antigens, i.e., which retain the antigen binding properties of two intact antibody molecules. While it is acknowledged that the prior art, especially the secondary references cited by the Examiner suggest that effective bi-specific antibodies can be obtained, the prior art does not anticipate functional bi-specific antibody dimers containing two intact antibody molecules. This outcome, i.e., that the subject antibody dimers bind two different antigens was not reasonably anticipated, especially when one considers the large size of the molecule, and that steric hindrances reasonably could have resulted in one antibody not retaining both antigen binding properties, or potentially neither. The fact that antibody multimeric exist naturally also does not suggest this outcome as these multimers do not comprise two different antibodies, which are genetically and or chemically modified to permit dimerization. Rather, such multimers are produced by spontaneous association of antibody molecules in vivo.

Thus, based on the foregoing, namely the complete failure of the prior art to teach or suggest the preparation of antibody heterodimers, as claimed, withdrawal of the §103 rejection based on Caron et al., Fanger et al., Cumber et al., Reff et al., Reff et al. and the Pierce Catalog is respectfully requested.

It is anticipated that this amendment should place this case in condition for allowance. A Notice to that effect is respectfully solicited.

Also, given the prolonged prosecution of this application, if any §112 issues remain, it would be appreciated if the Examiner would contact the undersigned telephonically to expedite resolution of this case.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____

Robin L. Teskin
Registration No. 35,030

1600 Tysons Blvd
McLean, Virginia 22102
(703) 905-2200 (Direct Dial)
(703) 905-2500 (Facsimile)

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APPENDIX

1. (Twice Amended) A method for producing an antibody heterodimer ~~composed~~ -comprised of two different antibody molecules each having binding specificity to two distinct antigens, from each other; wherein the method comprises:

(v) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has binding specificity to a first antigen when said heavy chain is paired with a corresponding light chain and introducing at least one cysteine codon via recombinant DNA mutagenesis, wherein the location of the cysteine does not interfere with the antigen binding properties of ~~the~~ said heterodimer;

(vi) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes ~~an~~ a corresponding antibody molecule light chain ~~of~~ having the same specificity as the heavy chain, to produce an intact first antibody molecule containing said introduced cysteine residue;

(vii) purifying said first intact antibody molecule from said host cell or expression system;

(viii) contacting said purified first intact antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and said introduced cysteine residue and thereby enhance the formation of antibody dimers when said reduced intact antibody molecular is contacted with a second intact antibody molecular; and

(ix) contacting the purified first intact antibody molecule with ~~another~~ a second intact antibody molecule having antigen specificity ~~other~~ different than the antigen specificity of the first antibody molecule purified in step (iii) and which second intact antibody contains a thiol reactive group and which does not have a cysteine group introduced therein; and allowing sufficient time for the dimerization reaction to proceed; thereby producing ~~said~~ an antibody heterodimer comprised of two intact antibody molecules each retaining their respective antigen binding specificity after dimerization.

[illegible] (Twice Amended) A method for producing an antibody heterodimer

(v) obtaining or constructing a DNA molecule that encodes an antibody molecule heavy chain that has binding specificity to a first antigen when paired with a complementary antibody light chain and introducing at least one cysteine codon therein via recombinant DNA mutagenesis, wherein the location of ~~the~~ said introduced cysteine does not interfere with the antigen binding properties of ~~the~~ said heterodimer;

(vi) expressing said DNA molecule in a suitable host cell, or expression system, together with a DNA molecule that encodes ~~an~~ said complementary antibody molecule light chain ~~of~~ having the same specificity as ~~the~~ said heavy chain, to produce an intact antibody molecule containing said introduced cysteine residue;

(vii) purifying said intact antibody molecule from said host cell or expression system;

(viii) contacting said purified antibody molecule with an amount of a suitable reducing agent sufficient to partially reduce the intra or inter molecular disulfide bonds of said antibody molecule and said introduce cysteine residue to thereby enhance the formation of antibody dimers; and

(v) adding a thiol reactive group onto ~~on another~~ a second intact antibody molecule having antigen specificity ~~other~~ different than the antigen specificity of the intact antibody molecule purified in step (iii) and which does not have a cysteine group introduced therein and allowing sufficient time for the dimerization reaction to proceed; thereby producing said antibody heterodimer comprised of two intact antibody molecules each retaining their respective different antigen binding specificity after dimerization.

28. (Twice Amended) An IgG IgG dimer produced by the method of Claim 2245, wherein said IgG's are of the same or different IgG subclass.

41. (Twice Amended) A pharmaceutical composition comprising an IgG IgG dimer according to Claim 2245, and a pharmaceutically acceptable carrier.

antigen to introduce a cysteine molecule ~~placed in~~ at a position which does not interfere with the antigen binding properties of said antibody heterodimer containing said IgG Mab and further inhibits or prevents formation of an intramolecular disulfide bridge between sister heavy chains on the same antibody molecule, reducing said introduced cysteine residue, and exposing said first intact Mab to a second intact IgG Mab having specificity to a different antigen then said first intact Mab and which comprises a thiol reactive group to produce said IgG IgG dimer comprised of two intact IgG molecules which respectively retain their different antigen binding specificity after dimerization.